DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 5/16/2008 has been entered.

Election/Restrictions

Newly submitted claims 23, 24 and 26 are directed to an invention that is independent or distinct from the invention originally claimed for the following reasons:

Claims 23 and 24 are placed in Group I of the restriction requirement dated 7/11/2005, that is, they are directed to an adenovirus vector comprising an immunoglobulin binding domain (i.e. *S. aureus* Protein A) inserted into the HI loop of the adenoviral fiber protein. In the reply dated 8/1/2005, applicants elected Group II, directed to such a vector with the immunoglobulin binding domain inserted into the carboxy terminal of the fiber protein, i.e. subject matter set forth in claims 25 and 26. There remains no generic linking claim regarding Groups I and II of the restriction requirement dated 7/11/2005. Group I is considered to be distinct from Group II and new Group IV for the same reasons et forth in the restriction requirement dated 7/11/2005.

Claim 25 is considered to be in original Group II of the restriction requirement dated 7/11/2005.

Claim 26 is in new Group IV.

Inventions II and III are directed to related products. The related inventions are distinct if: (1) the inventions as claimed are either not capable of use together or can have a materially different design, mode of operation, function, or effect; (2) the inventions do not overlap in scope, i.e., are mutually exclusive; and (3) the inventions as claimed are not obvious variants. See MPEP § 806.05(j). In the instant case, the inventions as claimed are mutually exclusive and thus are not obvious variants and have a different design, function, and effect. Furthermore, the inventions as claimed do not encompass overlapping subject matter and there is nothing of record to show them to be obvious variants. An adenoviral vector of claim 25, comprising a single chain antibody G28.5 would not read on such an adenoviral vector comprising a TNF-like domain of CD 40 ligand, and vice versa. Further, the subject matter of Group II has already been examined to a great extent (i.e previously pending claims 15 and 22) whereas the subject matter of Group IV has not.

Restriction for examination purposes as indicated is proper because all these inventions listed in this action are independent or distinct for the reasons given above and there would be a serious search and examination burden if restriction were not required because one or more of the following reasons apply:

(a) the inventions have acquired a separate status in the art in view of their different classification;

(b) the inventions have acquired a separate status in the art due to their recognized divergent subject matter;

(c) the inventions require a different field of search (for example, searching different classes/subclasses or electronic resources, or employing different search queries);

(d) the prior art applicable to one invention would not likely be applicable to another invention;

(e) the inventions are likely to raise different non-prior art issues under 35 U.S.C. 101 and/or 35 U.S.C. 112, first paragraph.

Since applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, claims 23, 24 and 26 are withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03.

Priority

Applicant's claim for the benefit of a prior-filed application under 35 U.S.C. 119(e) or under 35 U.S.C. 120, 121, or 365(c) is acknowledged. Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 119(e) as follows:

The later-filed application must be an application for a patent for an invention which is also disclosed in the prior application (the parent or original nonprovisional application or provisional application). The disclosure of the invention in the parent application and in the later-filed application must be sufficient to comply with the requirements of the first paragraph of 35 U.S.C. 112. See *Transco Products, Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir. 1994).

The disclosure of the prior-filed application, Application No. 60/398,057, fails to provide adequate support or enablement in the manner provided by the first paragraph of 35 U.S.C. 112 for one or more claims of this application. The '057 application fails to disclose single chain antibodies with a secretory leader sequence or a six-histidine tag. The first and only mention of these limitations of claim 25 are found in Example 6 of the instant application, 10/624,317: Example 6 is not found in the '057 application, which ends at Example 4. Neither the drawings nor the claims of the '057 application mention these claim limitations. Thus, the instant claim is given a priority date of 7/22/2003, the filing date of the instant application.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claim 25 is rejected under 35 U.S.C. 103(a) as being unpatentable over Wickham et al (U.S. Patent No. 5,962,311) and Meruelo et al (U.S. Patent No. 6,432,699, of record) in view of

Curiel et al (U.S. Patent No. 6,284,742), Francisco et al (J. Biol. Chem., 1997), and Fischer et al (Biotechnol. Appl. Biochem., 1999) and Ledbetter et al (5,182,368, of record). **This rejection is maintained, in part, for reasons set forth in the Office Action dated 11/16/2007, and for reasons set forth below.**

Wickham et al disclose a targeted recombinant adenovirus vector complex, wherein the vector complex comprises:

a) a gene encoding a modified fiber protein comprising a heterologous peptide domain, and

b) an epitope-specific, cell-targeting antibody,

wherein binding of the heterologous peptide domain to the epitope-specific, cell-targeting antibody connects the antibody to the modified fiber protein, thereby targeting the adenovirus complex to the desired cell recognized by the epitope-specific, cell-targeting antibody. The heterologous, non-native amino acid sequence confers upon the modified fiber protein the ability to bind, directly or indirectly, via a bispecific or multi-specific binding agent, such as an antibody or fragment thereof, to a target receptor or class of target receptors, preferably a cell-specific receptor. This interaction may be done by any means known in the art. The non-native amino acids may be introduced in the carboxy terminal portion of the fiber protein. See cols 9-10, joining ¶; col. 19, lines 5-17, 33-37). The antibody can be a single chain antibody (col. 11, lines 9-12).

Wickham et al do not disclose the modified fiber protein comprising the non-native amino acids to be an immunoglobulin-binding domain, specifically the immunoglobulin (IgG)-binding C domain from *S. aureus* Protein A, nor the use of the G28.5 single chain antibody.

Meruelo et al disclosed a targeted recombinant viral vector complex, wherein the vector complex comprises:

a) a recombinant adenovirus vector encoding a gene encoding a modified viral envelope protein comprising an immunoglobulin-binding domain, and

b) an epitope specific, cell-targeting antibody,

wherein binding of the immunoglobulin-binding domain to the antibody connects the antibody to the modified viral envelope protein, thereby targeting the adenovirus complex to the desired cell recognized by the epitope specific, cell-targeting antibody. Meruelo et al disclosed that the viral vector may be an adenovirus (col. 7, line 15; col. 8, lines 25-26), the immunoglobulin (IgG)-binding domain is from *S. aureus* Protein A, the viral vector and the desired antibody are pre-incubated prior to contacting the target cell (col. 7, lines 54-56), and because Protein A binds to an Fc region of antibody, these chimeric proteins enable one to use an antibody to target the viral particle to a desired cell to which the antibody binds (Figure 3A; col. 4, line 63, col. 5, line 4). Meruelo et al teaches specific embodiments wherein the virus has a modified envelope protein which utilizes the B domain of *S. aureus* Protein A:

"Protein A, a protein derived from *S. aureus*, has a strong affinity for the Fc region of various mammalian IgGs…Native protein A has five homologous IgG-binding domains (E, D, A, B and C)… (column 8, line 63 – column 9 line 5).

While Meruelo et al disclose that there are a large number of cell surface antigens suitable for use as acceptors and for which antibodies are already available (col. 7, lines 28-50), Meruelo et al do not teach the use of the G28.5 antibody, nor the insertion of the IgG-binding domain in the carboxy terminus of the fiber protein.

Curiel et al teach the desirability of targeting adenovirus to CD40-expressing dendritic cells in order to influence and increase the immune response (abstract, cols. 1 and 2). In order to target the adenoviral vectors to the dendritic cells, they were modified by binding a bi-specific antibody to the fiber protein, said antibody comprising G28.5, specific for CD40 (col. 2, lines 33-51, col. 3, lines 13-14).

Francisco et al teach that it is predictable to make single chain antibody molecules with high affinity for CD40 from the G28.5 antibody, and that CD40 is highly expressed on a number of malignancies and carcinomas. See the abstract, page 24165, second column, last ¶ to page 24166.

Fischer et al teach the expression of single chain antibodies in yeast as a preferred means for production of useful quantities of such antibodies. See the abstract and pages 117-118. Fischer et al teach the use of a secretory sequence and a His-6 tag for easy expression and purification of the single chain antibodies. See the ¶ linking pages 117-118, and page 118, second column, ¶ entitled "Cloning, transformation and selection".

Ledbetter et al teach that the G28.5 antibody can be ligated through its Fc domain to other molecules for targeting molecules to CD40-expressing cells (col. 6, lines 61-63 and col. 7, line 50 to col. 8, line 17).

It would have been obvious to one of ordinary skill in the art to substitute the heterologous amino acids of the modified fiber protein of Wickham et al with an immunoglobulin-binding domain, specifically a Fc-binding domain from *S. aureus* Protein A with a reasonable chance of success because the simple substitution of one known element for

another would have yielded predictable results to one of ordinary skill in the art at the time of the invention. An artisan would be motivated to substitute the heterologous peptide for an immunoglobulin-binding domain because Protein A has long been known in the art for its ability to bind the conserved Fc immunoglobulin domains of antibody molecules, and thus the recombinant adenoviral vector comprising a modified fiber protein comprising a Protein A immunoglobulin-binding domain would be advantageous for easily conferring easy cell-specific targeting properties with any one of an enormous genus artisan-desired cell-targeting antibodies, as taught by Meruelo et al. With respect to Meruelo's specific embodiments directed towards the use of the Protein A B domain, rather than the instantly claimed C domain, Meruelo teaches that Protein A comprises 5 homologous IgG binding domains (see above). It would have been obvious to the skilled artisan to exchange the B domain of Protein A with the C domain of IgG, because both domains are capable of binding the Fc domain of an antibody and thus can be used interchangeably in a predictable manner.

It also would have been obvious to substitute the cell-targeting antibodies of Wickham et al with the G28.5 antibody as taught by Curiel or Francisco et al with a reasonable chance of success because the simple substitution of one known element for another would have yielded predictable results to one of ordinary skill in the art at the time of the invention, and the teachings of Curiel and Francisco et al that targeting CD40-expressing cells is desirable therapeutically. It would have been obvious to modify the G28.5 single chain antibody of Francisco et al to include a secretory signal sequence and a His-6 tag because Fischer et al teach the predictable use of these components in order to produce and purify single chain antibodies. Finally, given the teachings of Meruelo et al that an Fc domain is required for binding to *S.*

aureus Protein A, and the teachings of Ledbetter et al that the G28.5 antibody can be ligated to other molecules via the Fc domain, it would have been obvious (or better said, necessary) to include an Fc domain in the single chain antibody in order to bind to the *S. aureus* Protein A domain within the fiber protein.

All of the claimed elements were known in the prior art, and one skilled in the art could have combined the elements as claimed by known methods with no change in their respective functions, and the combination would have yielded predictable results to one of ordinary skill in the art at the time of the invention (*See KERR International Co. v. Teleflex Inc.,* 82 USPQ2d 1385 (U.S. 2007)). People of ordinary skill in the art will be highly educated individuals, possessing advanced degrees, including M.D.'s and Ph.D.'s. They will be medical doctors, scientists, or engineers. Thus, these people most likely will be knowledgeable and well-read in the relevant literature and have the practical experience in molecular biology, cloning, virology, immunology and gene therapy. Therefore, the level of ordinary skill in this art is high.

At the time of the invention, those of ordinary skill in the art knew how to chemically and/or genetically modify viral capsid proteins, e.g. an adenovirus fiber protein, to comprise a heterologous amino acid domain that conferred, directly or indirectly, cell-specific targeting properties onto the viral vector. The ordinary artisan routinely practiced substituting one cell-specific targeting antibody for another cell-specific targeting antibody to be attached to the viral vector (e.g., Meruelo et al, col. 7, lines 28-50) so as to effectively (re)target the viral vector complex to a desired cell expressing an antigen recognized by the targeting antibody.

Given the teachings of the prior art and the level of skill of the ordinary skilled artisan at the time the instant invention was made, it must be considered that said ordinary skilled artisan would have had a reasonable expectation of success in practicing the claimed invention.

Response to Arguments

Applicant's arguments filed 5/16/2008 have been fully considered but they are not persuasive. Applicants essentially assert that the previously pending claims have been canceled, hence, the pending 35 USC 103 rejection was moot. This is not found persuasive because although the previous 35 USC 103 rejection has essentially been withdrawn, in light of the 35 USC 103 rejection set forth above the claims remain obvious in light of the prior art of record.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michael Burkhart whose telephone number is (571)272-2915. The examiner can normally be reached on M-F 8AM-5PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach can be reached on (571) 272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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